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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,653	11/15/2001	Avi J. Ashkenazi	P2730P1C38	4955

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,653	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/8/02 & 5/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment received 11/15/2001 has been entered in full.

2. Claims 1-118 are canceled

Claims 119-124 are pending and under examination.

Specification

3. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 310, line 13. Applicant is required to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

a. Claims 119-124 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility.

The claims are directed to antibodies that bind a polypeptide corresponding to SEQ ID NO:377, referred to in the specification as PRO1159. The utility and enablement of the antibody depends upon whether or not the polypeptide it binds has utility and enablement. The specification teaches that the nucleic acid of DNA60627-1508, which encodes the PRO1159 polypeptide was isolated from a blood granulocyte tissue library and thus, the DNA encodes a secreted factor (see page 366). The specification generally asserts that anti-PRO antibodies would be useful in diagnostic assays (see page 397-398) and the PRO1159 polypeptide is useful therapeutically where suppression of an immune response is beneficial (see pages 528-529). However, the specification does not disclose a nexus between any particular disease or disorder and the expression of the PRO1159 polypeptide.

The specification does not teach the expression of the polypeptide of PRO1159 in any specific tissue nor does the specification correlate the expression of PRO1159 with a specific disease state and the specification does not teach whether PRO1159 is

overexpressed or underexpressed in a specific disease state such that an antibody, which specifically binds PRO1159 would be useful diagnostically or for immunotherapy.

Applicant asserts that Example 155 at pages 528-529 of the specification at line 27, supports utility of the claimed invention. Example 155 of the specification is stimulatory activity in a mixed lymphocyte reaction (MLR) assay. However, the ability of a protein to stimulate lymphocyte proliferation in this assay does not support a specific and substantial utility for the claimed invention. The ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed PRO1159 polypeptide could be useful for the treatment of conditions where suppression of an immune response would be beneficial (page 528, lines 15-16) is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any.

Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between

responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one-way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-209, 246-247 of "Basic and Clinical Immunology," 1994. See also, "Manual of Clinical Laboratory Immunology," 6th Edition at pages 1164-1166.

Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Curr. Opin. Immunol. 4:553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67:1453-1460, 1999)

demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79:15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

Additionally, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibilty in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. When running the MLC assay for determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunlogy"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen

should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals, which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay, which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot

evaluate the conclusion. The specification states that "any decreases below control is considered to be a positive result for an inhibitory compound", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect an inhibitory effect in the MLC assay to correlate to a general inhibitory effect on the immune system, absent evidence to the contrary.

Therefore, the specification does not support a specific and substantial asserted utility or a well-established utility regarding the claimed antibodies because the PRO1159 polypeptide to which the antibodies bind does not have a specific and substantial asserted utility or a well-established utility. The proposed antibodies of the claimed invention are simply starting points for further research and investigation into potential practical uses of the PRO1159 polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

b. Claims 119 and 124 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 119 and 124 as written do not sufficiently distinguish the antibody over antibodies as they exist in nature because claims 119 and 124 do not particularly point out any non-naturally occurring differences between the claimed antibodies and the

structure of naturally occurring antibodies. The claimed antibody molecules read upon antibody molecules as they are naturally synthesized in eukaryotic cells such as in an individual with an autoimmune disease, for example.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1996)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F. Supp 68 (1967), 155 U.S.P.Q. 139, (District Court, New Jersey, 1967)). Amendemnt of the claims to recite "An isolated" or "purified" antibody or similar language would obviate this part (i.e., part b) of the rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 119-124 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 119 and 124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119 and 124 are indefinite for reciting "an antibody that binds" in claim 119 and "the antibody of claim 119 which specifically binds" in claim 124 because the exact meaning is unclear. It is not clear what the difference between the two claims is and what each claim is meant to encompass, given that antibody binding is determined by the variable regions structure and is a "specific" interaction.

9. Claims 119-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to an antibody that binds or specifically binds the polypeptide of SEQ ID NO:377 (i.e., PRO1159), wherein the antibody is monoclonal, humanized, an antibody fragment and labeled. The enablement of the antibody depends upon whether or not the polypeptide it binds has enablement.

The specification teaches that the nucleic acid of DNA60627-1508, which encodes the PRO1159 polypeptide was isolated from a blood granulocyte tissue library and thus, the DNA encodes a secreted factor (see page 366). The specification generally asserts that anti-PRO antibodies would be useful in diagnostic assays (see page 397-398) and the PRO1159 polypeptide is useful therapeutically where suppression of an immune response is beneficial (see pages 528-529). However, the specification does not disclose a nexus between any particular disease or disorder and the expression of the PRO1159 polypeptide.

The specification does not teach the expression of the polypeptide of PRO1159 in any specific tissue nor does the specification correlate the expression of PRO1159 with a specific disease state and the specification does not teach whether PRO1159 is overexpressed or underexpressed in a specific disease state such that an antibody, which specifically binds PRO1159 would be useful diagnostically or for immunotherapy.

The specification does not reasonably provide enablement for antibodies that bind the PRO1159 polypeptide from the written disclosure alone. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily

correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenetics, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Lewin B. (Genes VI, 1997, CH. 29, pp. 847-848) states "But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that overwhelming majority of regulatory events occur at the initiation of transcription" (see page 847, right column). These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled

at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic or therapeutic target are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the PRO1159 polypeptide expression, including the correlation to a diseased state, one of skill in the art would not be able to predictably use antibodies that bind the PRO1159 polypeptide as a diagnostic or therapeutic tool. The specification does not predict or show whether the PRO1159 polypeptide would be over-expressed or under-expressed in a specific, diseased tissue compared to the healthy tissue control. In the absence of a direct correlation between the up regulation of transcription and translation of the PRO1159 polypeptide associated with a disease state, one of ordinary skill in the art would be unable to use antibodies specific for the PRO1159 polypeptide.

No direction or guidance is provided to assist one skilled in the art to make and use the claimed antibodies that bind the PRO1159 polypeptide in any diagnostic or therapeutic setting. Thus, the proposed use of the claimed antibodies that bind the PRO1159 polypeptide are simply starting points for further research and investigation into potential practical uses of the polypeptide. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists

> in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the lack of predictability of the art to which the invention pertains as evidenced by Fu et al., Powell et al., Vallejo et al., Lewin B. and Jang et al., and lack of guidance in the specification related to using antibodies that bind or specifically bind the PRO180 polypeptide, undue experimentation would be required to practice the claimed antibodies with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective as a diagnostic or therapeutic tool correlated to a specific disease state.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER